RESPONSE

I. Status of the Claims

No claims have been cancelled. No claims have been amended. No new claims have been added.

Claims 1-6 are therefore presently pending in the case. For the convenience of the Examiner, a clean copy of the pending claims is attached hereto as **Exhibit A**.

II. Rejection of Claims 1-6 Under 35 U.S.C. § 101

The Action first rejects claims 1-6 under 35 U.S.C. § 101, as allegedly lacking a patentable utility. Applicants respectfully traverse.

As set forth in Applicants' response submitted on November 12, 2002 ("the pervious response") to the First Office Action in this case, which was mailed from the Office on August 14, 2002 ("the First Action"), the present sequence has a number of patentable utilities, among them, as detailed in the specification as originally filed, on page 3, lines 7-9, in "the identification of protein coding sequence". This is evidenced by the fact that SEQ ID NO:1 can be used to map the 13 coding exons on chromosome 1 (present within GenBank Accession Number AL356356, which is a clone from human chromosome 1; alignment and first page from GenBank record shown in **Exhibit B**). The specification details, at page 3, lines 12-14, that the present sequence "identify biologically verified exon splice junctions, as opposed to splice junctions that may have been bioinformatically predicted from genomic sequence alone". It is well known that intron/exon boundaries are mutational hot spots, and thus the identification of the actual splice sites is of great utility to the skilled artisan. The specification details, from page 11, line 30 to page 12, line 4, that "sequences derived from regions adjacent to the intron/exon boundaries of the human gene can be used to design primers for use in amplification assays to detect mutations within the exons, introns, splice sites (*e.g.*, splice acceptor and/or donor sites), *etc.*, that can be used in diagnostics and pharmacogenomics". Applicants respectfully submit that the practical scientific value of biologically validated, expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Although Applicants need only make one credible assertion of utility to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re*

Gottlieb, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), as yet a further example of the utility of the presently claimed polynucleotides, as described in the specification at least at page 3, line 9, the present nucleotide sequence has a specific utility in mapping the protein encoding regions of the corresponding human chromosome, specifically chromosome 1, as described in the specification at least on page 3, lines 10-12 and page 17, lines 20-21. This is evidenced by the fact that SEQ ID NO:1 can be used to map the 13 coding exons on chromosome 1, as detailed above (**Exhibit B**). Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of human chromosome 1 that contains the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequences. In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence. For further evidence in support of the Applicants' position, the Examiner is invited to review, for example, section 3 of Venter *et al.* (2001, Science *291*:1304, at pp. 1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article.

Applicants respectfully remind the Examiner that only a minor percentage (2-4%) of the genome actually encodes exons, which in-turn encode amino acid sequences. The presently claimed polynucleotide sequence provides biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* define that portion of the corresponding genomic locus that actually encodes exon sequence, as described above. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

The Action questions these asserted utilities, stating that "an extremely large number of

markers for human DNA already exist" (Action at page 3). The Examiner seems to be confusing the requirements of a **specific** utility with a **unique** utility. The fact that a small number of other nucleotide sequences could be used to map the protein coding regions in this specific region of chromosome 1 does not mean that the use of Applicants' sequence to map the protein coding regions of chromosome 1 is not a specific utility. As clearly stated by the Federal Circuit in *Carl Zeiss Stiftung v. Renishaw PLC*, 20 USPQ2d 1101 (Fed. Cir. 1991):

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding a lack of utility." *Envirotech Corp. v. Al George, Inc.*, 221 USPQ 473, 480 (Fed. Cir. 1984)

In other words, Applicants' sequence does not have to be the **only** sequence capable of providing such a utility. The requirement for a **specific** utility, which is the proper standard for utility under 35 U.S.C. § 101, should not be confused with the requirement for a **unique** utility, which is clearly an improper standard. If every invention were required to have a unique utility, the Patent and Trademark Office would no longer be issuing patents on batteries, automobile tires, golf balls, golf clubs, and treatments for a variety of human diseases, just to name a few particular examples, because examples of each of these have already been described and patented. However, only the briefest perusal of any issue of the Official Gazette provides numerous examples of patents being granted on each of the above compositions every week. Furthermore, if a composition needed to be unique to be patented, the entire class and subclass system would be an effort in futility, as the class and subclass system serves solely to group such common inventions, which would not be required if each invention needed to have a unique utility. Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

The present invention has a number of additional substantial and credible utilities, not the least of which is, as described in the specification on page 6, lines 16-18, that the present nucleotide sequences have utility in assessing gene expression patterns using high-throughput DNA chips. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501 and 6,261,776. As the present sequences are specific markers of the human genome (see above), and such specific markers are targets for the discovery of drugs that are associated with human disease, those of skill in the art would instantly recognize that the present nucleotide sequences would be an ideal, novel candidate for assessing gene expression using such DNA

chips. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequences, must in themselves be useful.

The Action also questions this utility, stating that "Applicants have also not identified any particular reason for the use of this particular polynucleotide to analyze gene expression using "DNA chips" (Action at page 3). First, Applicants point out that nucleic acid sequences are commonly used in gene chip applications without any information regarding the function of the encoded protein, or even evidence regarding whether the sequence is actually even expressed. Thus, the present sequence, which has been biologically validated to be expressed, has a much greater utility than sequences that are merely predicted to be expressed based on bioinformatic analysis. Additionally, Applicants point out that nucleic acid sequences such as SEQ ID NO:1 are routinely used by companies throughout the biotechnology sector **exactly** as they are presented in the Sequence Listing, without **any** further experimentation. Expression profiling does **not** require a knowledge of the function of the particular nucleic acid on the chip - rather the gene chip indicates which DNA fragments are expressed at greater or lesser levels in two or more particular tissue types. Furthermore, although further information regarding the biological activity of a particular nucleic acid sequence might make it even more useful in gene chip applications, this does not mean that the use of the presently claimed nucleic acid sequence in gene chip applications is not a specific utility (*Carl Zeiss Stiftung v. Renishaw PLC, supra*).

Importantly, it has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974; "*Langer*"); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA, 1971). As clearly set forth in *Langer*:

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

Langer at 297, emphasis in original. As set forth in the MPEP, "Office personnel must provide evidence sufficient to show that the statement of asserted utility would be considered 'false' by a person of ordinary skill in the art" (MPEP, Eighth Edition at 2100-40, emphasis added). Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

In addition, Applicants point out that a sequence sharing greater than 99% identity at the

protein level over a large portion of the claimed sequence is present in the leading scientific repository for biological sequence data (GenBank), and has been annotated by third party scientists *wholly unaffiliated with Applicants* as "Homo sapiens thrombospondin repeat containing 1 (TSRC1)" (GenBank accession number NM_019032; alignment and GenBank report provided in **Exhibit C**). Furthermore, additional third party scientists *wholly unaffiliated with Applicants* have described the full length murine homolog of the human TSRC1 sequence, and this sequence shows an expected 74% identity and 79% similarity at the protein level over the complete length of Applicants' sequence (GenBank accession number AY158701; alignment and GenBank report provided in **Exhibit D**). Given these GenBank annotations, it is clear that those skilled in the art would clearly believe that Applicants' sequence is a thrombospondin repeat containing protein, specifically the human TSCR1 sequence.

The scientists that described the murine TSRC1 report that the murine and human TSRC1 likely arose from a chromosomal inversion that interrupted an ancestral ADAMTS gene (Buchner and Meisler, Gene 307:23-30, 2003; "Buchner and Meisler"; abstract presented in **Exhibit E**). In the specification as originally filed, Applicants noted the similarity of the present sequence to "the ADAMTS family of secreted proteases" (specification at page 2, lines 8-9), which are well known to contain thrombospondin repeats (hence, the "TS" designation). Furthermore, SMART analysis of the amino acid sequence encoded by SEQ ID NO:1 (Letunic et al., Nucl. Acids Res. *30*:242-244, 2002) indicates that Applicants' claimed protein has four thrombospondin repeat domains (denoted in the SMART analysis as TSP1; **Exhibit F**). Buchner and Meisler report that the murine TSCR1 sequence contains seven thrombospondin repeats, is expressed in all fetal and adult tissues, and that the human gene encodes a protein of 1076 amino acids (see **Exhibit E**). The specification as originally filed indicates that the presently claimed human sequence (877 amino acids) is expressed in a subset of human tissues, including "pituitary, lymph node, bone marrow, small intestine, colon, skeletal muscle, uterus, placenta, mammary gland, bladder, cervis, fetal kidney and fetal lung" tissues (specification at page 4, lines 1-4). Thus, information in Buchner and Meisner is completely consistent with Applicants sequence being a splice variant of the human TSCR1 gene, which is differentially expressed in certain tissues. Applicants respectfully point out that the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be believable. Applicants submit that the skilled artisan would believe that Applicants' sequence is a human TSCR1 sequence, and would thus readily understand the utility of the presently claimed

sequence, as described above, particularly in gene chip applications. As this is the standard for meeting the utility requirement of 35 U.S.C. § 101, Applicants submit that the present claims must clearly meet the requirements of 35 U.S.C. § 101.

Finally, as set forth in the previous response, the requirements set forth in the Action for compliance with 35 U.S.C. § 101 do not comply with the requirements set forth by the Patent and Trademark Office ("the PTO") itself for compliance with 35 U.S.C. § 101. While Applicants are well aware of the new Utility Guidelines set forth by the USPTO, Applicants respectfully point out that the current rules and regulations regarding the examination of patent applications is and always has been the patent laws as set forth in 35 U.S.C. and the patent rules as set forth in 37 C.F.R., not the Manual of Patent Examination Procedure or particular guidelines for patent examination set forth by the USPTO. Furthermore, it is the job of the judiciary, not the USPTO, to interpret these laws and rules. Applicants are unaware of any significant recent changes in either 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit that is in keeping with the new Utility Guidelines set forth by the USPTO. This is underscored by numerous patents that have been issued over the years that claim nucleic acid fragments that do not comply with the new Utility Guidelines. As examples of such issued U.S. Patents, the Examiner is invited to review U.S. Patent Nos. 5,817,479, 5,654,173, and 5,552,281 (each of which claims short polynucleotides), and recently issued U.S. Patent No. 6,340,583 (which includes no working examples), none of which contain examples of the "real-world" utilities that the Examiner seems to be requiring. As issued U.S. Patents are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph (see Section V, below), Applicants submit that the present polynucleotides must also meet the requirements of 35 U.S.C. § 101. While Applicants understand that each application is examined on its own merits, Applicants are unaware of any changes to 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit, since the issuance of these patents that render the subject matter claimed in these patents, which is similar to the subject matter in question in the present application, as suddenly non-statutory or failing to meet the requirements of 35 U.S.C. § 101. Thus, holding Applicants to a different standard of utility would be arbitrary and capricious, and, like other clear violations of due process, cannot stand.

For each of the foregoing reasons, Applicants submit that as the presently claimed nucleic acid molecules have been shown to have a substantial, specific, credible and well-established utility, the rejection of claims 1-6 under 35 U.S.C. § 101 has been overcome, and request that the

rejection be withdrawn.

III. Rejection of Claims 1-6 Under 35 U.S.C. § 112, First Paragraph

The Action next rejects claims 1-6 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by a specific, substantial, and credible utility or a well-established utility. Applicants respectfully traverse.

Applicants submit that as claims 1-6 have been shown to have "a specific, substantial, and credible utility", as detailed in section II above, the present rejection of claims 1-6 under 35 U.S.C. § 112, first paragraph, cannot stand.

Applicants therefore request that the rejection of claims 1-6 under 35 U.S.C. § 112, first paragraph, be withdrawn.

IV. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner Swope have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

July 7, 2003
Date

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